Trends in Survival of Patients With Hepatocellular Carcinoma Between 1977 and 1996 in the United States

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The recent increase in the incidence of hepatocellular cancer in the United States is thought to underlie the rising mortality of this malignancy. However, it remains unknown whether survival of patients with hepatocellular carcinoma (HCC) has changed during the same time period. Using the SEER database (Surveillance, Epidemiology, and End Results) of the National Cancer Institute, we examined the temporal changes and determinants of survival among patients with histologically proven HCC over a 20-year period. Between 1977 and 1996, 7,389 patients diagnosed with HCC were followed in the survival database of SEER. The overall 1-year relative survival rate increased from 14% (95% confidence intervals (CI): 12-16) during 1977-1981 to 23% (95% CI: 21-24) during 1992 to 1996. Between the same two time periods, less improvement was seen in the 5-year survival rates, which increased from 2% (95% CI: 1-3) to only 5% (95% CI: 4-7). The median survival increased slightly from 0.57 years during 1977 to 1981 to 0.64 years during 1992 to 1996. In general, there were no significant differences in survival between men and women or between ethnic groups. During 1987 to 1991, a small fraction (0.8%) of patients underwent radical surgery; these patients had 1-year survival of 59% (95% CI: 35-83%), and 5-year survival of 35% (95% CI: 12-58%). Similar rates were seen during 1992-1996. In conclusion, a small improvement in survival of patients with HCC was seen between 1977 and 1996. Most of this apparent benefit is restricted to the first year following cancer diagnosis, raising the possibility of lead-time bias. There were no significant differences related to gender or ethnicity. (HEPATOLOGY 2001;33:62-65.)

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver.[1] A recent increase in the age-adjusted mortality rates of HCC was reported in the United States.[2] Marked ethnic and gender-related differences in mortality were noted; men were 3 times more affected than women and minority ethnic groups were affected several times more than white patients.[2] Mortality rates of HCC are affected by its incidence as well as by survival after diagnosis. Although the age-adjusted incidence rates of HCC have been increasing during the same time period of rising mortality, the temporal and demographic features of survival in patients with HCC in the United States are unknown. In the last 2 decades, management of patients with HCC has included variable application of screening and treatment modalities such as ultrasound, computed tomography scan, α-fetoprotein, hepatic resection, chemoembolization, or alcohol injection.[3] The effectiveness of the current overall management of patients with HCC in reducing mortality remains unknown.

In the United States, the Surveillance, Epidemiology, and End Results (SEER) Program is an ongoing contract-supported program of the National Cancer Institute to collect population-based cancer incidence and survival data in a uniform cancer registry. Using the SEER database, we examined the temporal changes as well as determinants of survival in patients with HCC over a 20-year period.

PATIENTS AND METHODS

Database. The National Cancer Institute's SEER Program consists of 9 population-based cancer registries. The study population was selected from the 9 population-based cancer registries that constitute the National Cancer Institute's SEER Program. The registries account for 10% to 14% of the US population and include the states of Connecticut, Hawaii, New Mexico, and Utah and the metropolitan areas: San Francisco/Oakland, Detroit, Seattle, and Atlanta. Information pertaining to the incidence and survival of all types of cancer between 1974 to 1996 are available on a CD-ROM issued by the National Cancer Institute.[4] The ninth revision of the *Clinical Modification of the International Classification of Diseases* (ICD-9-CM) and *International Classification of Diseases for Oncology* (*ICD-O*)[5] are used to encode for malignancies in SEER incidence data. The SEER Program collects information on demographic characteristics of patients, anatomic site of the malignancy, histologic cell type, stage of the disease at time of diagnosis, treatment, and follow-up, including survival status.

Study Population. We analyzed information from all patients diagnosed between 1977 and 1996 with histologically confirmed HCC (ICD-O code 8170).

Statistical Analyses. Cohorts of patients with HCC were analyzed in 5 yearly intervals (1977-1981, 1982-1986, 1987-1991, and 1992-1996). For each of these intervals, we calculated the observed, expected, and relative survival rates at monthly intervals for 5 years after HCC diagnosis. The observed survival rate was calculated using standard life table procedures and represents the proportion of patients surviving for a specified length of time after cancer diagnosis. The expected survival rate is based on the mortality rate for the total population after taking into account age, sex, ethnicity, and calendar year of diagnosis of the patients. The relative survival rate is calculated by adjusting the observed survival for expected mortality for a cancer-free cohort using a procedure described by Ederer et al.[6] The median observed survival was also calculated.

Abbreviations: HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval.

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TABLE 1. Observed and Relative Survival Rates of Patients Diagnosed With HCC in the SEER Database Between 1977 and 1996

	(%) Observed Survival at 1 Year	95% CI	(%) Relative Survival at 1 Year	95% CI	(%) Observed Survival at 5 Years	95% CI	(%) Relative Survival at 5 Years	95% CI
1977-1981 (n = 1,193)	13%	(11-15)	14%	(12-16)	2%	(1-3)	2%	(1-3)
1982-1986 (n = 1,560)	15%	(13-17)	15%	(14-17)	3%	(2-4)	4%	(3-5)
1987-1991 (n = 2,063)	18%	(16-20)	19%	(17-21)	4%	(3-5)	5%	(3-6)
1992-1996 (n = 2,573)	22%	(20-24)	23%	(21-24)	5%	(4-7)	6%	(4-8)

NOTE. $P < .0001$ for overall differences in observed or relative survival rates between the 4 cohorts.

Survival rates were calculated for the entire group as well as for subgroups based on gender (men vs. women), ethnicity (white, black, other), stage of disease at diagnosis (localized, focal spread, and distant), and treatment (surgical vs. nonsurgical). Surgical treatment was recorded as either "radical" or "palliative." Survival rates were also calculated for 3 age groups: below 40 years, between 40 and 60, and above 60 years. The database does not contain information regarding management of patients in the "nonsurgical" group.

The 95% confidence intervals (CI) were calculated for all observed and relative survival rates. The differences between any two survival rates were considered significant if their 95% CI did not overlap. In addition, χ^2 tests were used to assess the differences between multiple rates in independent groups. Calculations were performed using the SEER*Stat version 2.0, which is the statistical package created for the analysis of the SEER database.[4]

RESULTS

During the time period between 1977 and 1996, 7,398 patients were identified with histologically proven HCC in the SEER database. The majority of these patients had complete follow-up (93.3%). Most were men (75%) and the overall ethnic distribution was as follows: 65% white, 14% black, and 21% designated as "other." This latter category is a heterogeneous group that includes Native Americans, Pacific Islanders, and Asians.

The 1-year and 5-year observed and relative survival rates of patients with HCC are shown in Table 1. Both observed and relative survival rates were very similar. The overall 1-year relative survival rate increased significantly from 14% (95% CI, 12-16) during 1977 to 1981 to 23% (95% CI, 21-25) during 1992 to 1996. A smaller increment in survival was recorded at 5 years. The 5-year relative survival rate increased from 2% (95% CI, 1-3) during 1977 to 1981 to only 6% (95% CI, 4-8) during 1992 to 1996. The statistical significance is evident by the nonoverlapping 95% CI. The overall median survival increased from 0.57 years during 1977 to 1981 to 0.64 years during 1992 to 1996.

In Figure 1, the observed survival rates are displayed for cohorts of patients diagnosed with HCC during each 5-year period between 1977 and 1996. Although survival rates have increased progressively from 1977 to 1996, most of the improvement, however, was noted early within the first year after HCC diagnosis. By the fourth and fifth years after diagnosis, the survival curves of all cohorts converge and the absolute differences between the adjacent curves became much less significant.

Surgical procedures were recorded only during the last 10 years of the study (1987-1996). "Radical" surgery denoted partial or removal of primary site plus partial or removal of other organs. "Palliative" surgery, on the other hand, denoted partial removal of primary site, debulking surgery, or surgery not otherwise specified. Other technical surgical details were not kept in the database. During 1987 to 1991, 0.8% and 7.4% of all patients with HCC underwent either radical or palliative surgery, respectively. For those who had radical surgery, the 1-year relative survival was 60% (95% CI, 36-84), and the 5-year relative survival rate was 40% (95% CI, 14-66). Patients who underwent palliative surgery had a 1-year survival of 50% (95% CI, 41-58) and 5-year survival of 20% (95% CI, 12.8-27.2). Despite the trend towards longer survival with radical surgery, the 95% CI were wide and overlapping. The median survival was prolonged to 21 months for radical surgery and 12 months for palliative surgery. During 1992 to 1996, these proportions did not change significantly with 0.8% and 8.3% of patients having radical or palliative surgery, respectively. The 1-year survival was 63% for those who underwent radical surgery and 70% for palliative surgery, $P > .05$. The use of screening, tumor embolization, chemoembolization, or percutaneous injection of alcohol was not specifically recorded.

The observed and relative survival rates for patients with HCC were calculated for whites and blacks during each of the 5-year periods between 1977 and 1996. Relative survival rates for patients diagnosed during 1992 to 1996 are shown separately for men and women in Fig. 2. There were no significant differences in survival between white, black, or "other" patients with HCC at 1 year, 2 years, and 5 years as evidenced by the overlapping values of the 95% CI. In addition, survival rates were not different between men and women (Fig. 2). Similarly, no significant differences in survival related to gender or ethnicity were seen during the earlier time periods (1977 to 1991).

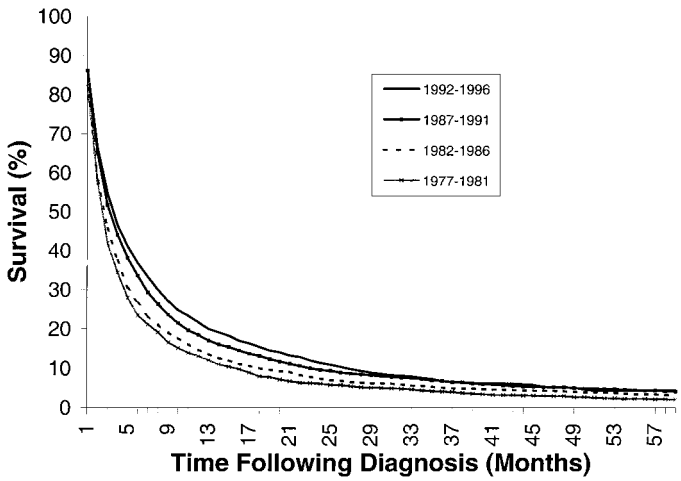

FIG. 1. The observed survival rates within the first 5 years after the diagnosis of HCC. Each curve represents survival among patients diagnosed in a 5-year period between 1977 and 1996. Early "apparent" improvement in survival all but vanishes by the end of 5-year follow-up.

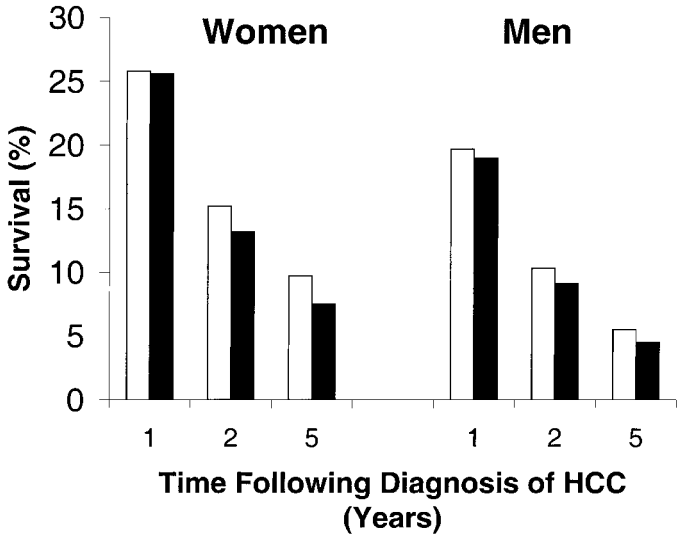

FIG. 2. The 1-year, 2-year, and 5-year survival rates of patients diagnosed with HCC between 1992 to 1996 broken down by gender and ethnicity. (□), White patients; (■), black patients.

During 1977 to 1981 and 1982 to 1986, survival rates of persons below age 40 were significantly longer than those of older patients (Table 2). For example, during 1982 to 1986, the 1-year survival was 32% (95% CI, 21-43) among patients below 40 years compared with 13% (95% CI, 11-15) in those above age 60, $\chi^2 = 16.8$, $P < .0001$. These age-related differences became nonsignificant (for 1-year survival) and less significant (5-year survival) during 1987 to 1991 and 1992 to 1996. This closing gap in age-related survival resulted mainly from improved survival among patients older than 40 during 1987 to 1991 and 1992 to 1996. On the other hand, survival among patients younger than 40 did not improve in more recent cohorts. Although the *P* values pertain to overall differences between several rates, differences between any two rates are better assessed by observing the overlap between 95% CI.

Survival rates were significantly different depending on the recorded stage of the malignancy at the time of diagnosis: localized, focal spread, and distant spread. A "localized" tumor was defined as an invasive neoplasm confined entirely to the organ of origin. A "regional" tumor was defined as a neoplasm that has extended beyond the limits of the organ of origin directly into surrounding organs or tissues, into regional lymph nodes, or both direct extension and regional lymph node involvement. A "distant" tumor was defined as a neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis. Of all patients, 24.8% had local HCC, 23.6% had focal HCC, and the rest were either distant or unclassified. In general, patients younger than 60 years were more likely to have localized or regional disease than older patients (data not shown). In turn, patients with localized disease were significantly more likely to undergo surgical treatment, either palliative or radical (21%), than those with regional disease (7%) (Table 3). The great majority (97%) of patients with advanced "distant" disease did not undergo any kind of surgery.

TABLE 3. The Number of Patients With Different Stages of HCC Who Underwent Radical or Palliative Surgery

	Localized HCC [%]	Regional Spread Only [%]	Rest	Total
Radical surgery	24 [1.7%]	6 [0.4%]	13 [0.4%]	43
Palliative surgery	278 [19.1%]	94 [6.7%]	88 [29.1%]	460
No surgery	1,152 [79.2%]	1,302 [92.9%]	2,914 [92.5%]	5,368
Total	1,545	1,402	3,015	5,871
%	24.8%	23.9%	51.4%	100%

DISCUSSION

The current results have shown that despite a statistically significant improvement in survival rates between 1977 and 1996, patients with HCC continue to have a dismal median survival of approximately 7 months. There were no differences in survival related to gender or ethnicity and only a weak trend towards longer survival in younger patients that did not persist among more recent cohorts. Less than 1% of all patients with HCC underwent radical surgery resulting in their prolonged survival to a median of approximately 21 months.

The survival improvement noted in this study among the more recent cohorts of patients with HCC was largely restricted to the first year after HCC diagnosis. On the other

TABLE 2. One and 5-Year Relative Survival Rates Among Patients Diagnosed With HCC in the SEER Database Presented for 5-Year Periods Between 1977 and 1996

Age		1977-1981	1982-1986	1987-1991	1992-1996	*P*
20-39	Total cases (n)	55	71	69	73	
	1 year survival (%)	41.3 (28.0-54.6)	31.9 (20.8-43.0)	26.1 (15.5-36.7)	22.6 (12.5-32.7)	.0873
	5 year survival (%)	9.4 (1.4-17.4)	14.0 (5.5-22.5)	10.2 (2.6-17.8)	NA	.9397
	Median survival (year)	0.85	0.73	0.68	0.65	
40-59	Total cases (n)	280	398	516	660	
	1 year survival (%)	14.3 (10.1-18.5)	17.5 (13.7-21.3)	18.3 (14.9-21.7)	24.8 (21.4-28.2)	.0005
	5 year survival (%)	2.1 (0.4-3.8)	3.9 (1.9-5.9)	4.9 (3.0-6.8)	7.1 (4.1-10.1)	.0169
	Median survival (year)	0.58	0.61	0.61	0.67	
>60	Total cases (n)	858	1,091	1,478	1,840	
	1 year survival (%)	10.8 (8.7-12.9)	12.8 (10.8-14.8)	17.8 (15.8-19.8)	20.9 (19.0-22.8)	<.0001
	5 year survival (%)	1.4 (0.6-2.2)	2.1 (1.2-3.0)	3.0 (2.1-3.9)	4.5 (2.7-6.3)	<.0001
	Median survival (year)	0.56	0.57	0.61	0.63	
P	1 year survival	<.0001	<.0001	.2487	.1174	
	5 year survival	<.0001	<.0001	.0080	.0120	

hand, the absolute differences in the 5-year survival between cohorts from different times were very small. This discrepancy between early improvement followed by an unchanged long-term survival in recent cohorts is consistent with lead-time bias. More HCC are detected early presumably as a result of increased or improved screening. Lead-time is the interval from the point of detection by a screening test to the usual point of diagnosis in the absence of screening.[7] The additional survival associated with lead-time is termed "lead-time bias" and it indicates an artifactual survival improvement. On the other hand, survival trends among the minority of patients who underwent radical surgery represent a true increase in survival. As opposed to lead-time bias, the marked improvement in survival in these patients was mainly gained during the first year of diagnosis but remained high thereafter. These results indicate that once complete removal of HCC is achieved in the absence of early spread and recurrence, the risk of late recurrence is low.

At present, complete surgical resection or liver transplantation offers the potential curative therapy for patients with HCC.[3] Radical surgery was reported in less than 1% of patients. The exact nature of these operations and whether resection was accompanied by transplantation cannot be discerned from the database and potential random misclassification between radical and palliative operations cannot be ruled out. Nevertheless, the combined total of patients who underwent any surgery was less than 8%. Survival was significantly better among patients receiving any kind of surgery. Part of the improved survival with surgery might be a result of selection bias. Typical surgical patients have localized HCC disease, compensated cirrhosis, and no significant comorbid illnesses; these patients probably have a better prognosis irrespective of surgery. Most HCC cases develop within cirrhotic livers and the risk of HCC increases progressively with advanced cirrhosis.[8] By the time of HCC diagnosis, the presence of advanced cirrhosis, large tumor size, or distant spread limit the number of patients eligible for curative surgery.[9] In this study, having localized HCC was the only significant predictor of surgical treatment.

The current study has several strengths. Only patients with histologically confirmed HCC were included in the analyses. A complete long-term follow-up for the majority of patients was possible. The large diverse population of HCC patients is representative of the whole United States. Therefore, the results of this study reflect the overall survival outcomes of patients and reflect the effectiveness of HCC management in patient survival. These results therefore might differ from single center experience. For example, a study from 4 hospitals in Los Angeles, CA reported an overall median survival of 18 months among 121 patients with HCC who were seen between 1976 and 1982.[10] On the other hand, previous non-US population–based studies showed similar results. A recent European study reported survival rates from population-based cancer registries in 17 European countries.[11] The investigators reported a 1-year relative survival rate of 16% and a 5-year survival of 5%. The 1-year survival varied form 7% in Denmark to 20% in Spain. Survival rates were not different between men and women and were slightly higher in the youngest age groups in most countries. Similar to the US results reported in our study, survival rates have improved significantly between 1978 and 1989 but remained relatively low. When comparing 1978 to 1980 with 1987 to 1989, the weighted average 1-year survival for European patients with primary liver cancer increased from 8% (95% CI, 7-10) to 18% (95% CI, 15-21). Less changes were noted in 5-year relative survival rate, which remained very poor: 6% (95% CI, 4-9) during 1987 to 1989.[11] A slightly higher 5-year survival rate (9%) was estimated for the period 1987 to 1989 in Osaka, Japan.[12]

It was not possible in this study to identify patients who underwent screening for HCC, or patients who received non-surgical treatment such as embolization, chemoembolization, or percutaneous alcohol injection. However, the small improvement in the overall long-term survival suggests that these modalities are either ineffective or applied on too narrow a scale to change the overall trends in survival. The rising incidence of HCC in the United States is likely to continue for a few more years,[2,13] and large outcomes trials are needed to examine the effectiveness of HCC screening and treatment strategies on the long-term survival of patients with HCC.

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